neurotrophic factor withdrawal. In addition, Par-4, has been found to specifically interact with the regulatory domain of atypical protein kinase C subfamily of isoenzymes (aPKCs), which dramatically inhibits their enzymatic activity (Diaz-Meco *et al.*, Cell 86:777-786 (1996)).--

Please replace the paragraph, beginning at page 10, line 8, with the following rewritten paragraph:

--Figures 15A and 15B show the nucleotide sequence of a human Par-4 promoter region and open reading frame (SEQ ID NO: 8). An intron is indicated by bold type and the Par-4 protein open reading frame is in bold and underlined.--

Please replace the paragraph, beginning at page 16, line 4, with the following rewritten paragraph:

--"Carrier" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™; polyethylene glycol (PEG); and PLURONICS™ block copolymers.--

Please replace the paragraph beginning at page 17, line 17, with the following rewritten paragraph:

--Nucleic acid encoding a native human Par-4 protein is known in the art (PCT Publication WO 98/13494, GenBank Accession No: U63809), and is shown in Figure 11A (SEQ ID NO: 1). The encoded amino acid sequence (SEQ ID NO: 2) is shown in Figure 11B and the

5' untranslated region of Par-4 including a portion of the promoter sequence is shown in Figure 14 (SEQ ID NO: 7). Recently we have cloned and sequenced the entire Par-4 promoter region, which is shown in Figures 15A and 15B along with the beginning of the coding region (SEQ ID NO: 8).--

Please replace the paragraph beginning at page 18, line 24, with the following rewritten paragraph:

--At least one intron, identified in bold in Figure 15B, is located in the Par-4 promoter. This intron is located in the 5' untranslated region and was identified by comparing the gene sequence with a Par-4 cDNA sequence.--

Please replace the paragraph beginning at page 34, line 13, with the following rewritten paragraph:

--Recruitment of endogenous components of the TNFR-1 signaling complex upon cell stimulation with TNFα has previously been demonstrated (Hsu *et al.*, Immunity 4:387-396 (1996); and McCarthy *et al.*, J. Biol. Chem., 273:16968-16975 (1998)). To examine the involvement of PS1 in TNFα-induced NF-κB activation, endogenous PS1 was immunoprecipitated at various time points from lysates of TNFα-treated and TNFα-untreated 293HEK cells. The immunoprecipitates were examined by immunoblot with an anti-RIP antibody. Briefly, subconfluent cultures of 293HEK cells were stimulated or not with 40ng/ml recombinant human TNFα (Calbiochem). Cells were then washed twice with ice cold PBS and lysed in 1 ml of lysis buffer (50 mM HEPES, 150 mM NaCl, 2 mM EDTA, 0.1% Nonidet P-40, 10 mM Na_3VO_4, and COMPLETE™ protease inhibitor mixture (Boehringer Mannheim). Cells were lysed on ice for 15 minutes then centrifuged at 14,000 rpm for 20 minutes and the supernatants were collected. Lysates were then normalized such that equivalent amount of protein was present in each sample using the bicinchonic acid (BCA) method (Pierce). Lysates were pre-cleared for 2 hours with rabbit pre-immunization serum (5 μg) and 30 μl Protein-G agarose beads (Boehringer Mannheim). The lysates were then immunoprecipitated with 10 μg monoclonal anti-PS1 antibody. The immunoprecipitates were then washed five times in lysis buffer. Samples were resolved on 8% NuPage Tris-Glycine gels (Novex), transferred to PVDF

membrane (Millipore) and subjected to Western blot analysis with an anti-RIP polyclonal antibody (Sigma).--

Please replace the paragraph beginning at page 37, line 18, with the following rewritten paragraph:

--Par-4 expression is enhanced in cells expressing PS1 mutations (PS1-FAD), and specifically inhibits the enzymatic activity of the aPKCs. As demonstrated in Figure 4C, Par-4 severely abrogated PS1 induced NF-κB activation. The aPKCs are key regulators of NF-κB activity and are negatively regulated by Par-4 (Diaz-Meco *et al.*, Cell 86:777-786 (1996)). Together with the evidence presented here that Par-4 impairs PS1-induced NF-κB activation (Figure 4C), this strongly suggests that increased expression of Par-4, following an apoptotic insult, could be sufficient to inhibit NF-κB survival-signaling, thereby sensitizing PS1-FAD expressing cells to the induction of apoptosis. To address this possibility, Par-4 mRNA levels in the stable PC12 cell lines were determined following exposure to an apoptotic insult. Par-4 mRNA levels were analyzed by quantitative real-time PCR. Briefly, total RNA was analyzed using an ABI PRISM™ 7700 Sequence Detection System (PE Applied Biosystems). RNA was extracted and purified from PC12 cell cultures using the RNAqueous kit (Ambion Inc.) according to manufacturer's instructions. Aliquots of RNA (2 μg) were reverse-transcribed using Multiscribe Reverse Transcriptase (PE Applied Biosystems). Sequence-specific primers and probes were designed using Primer Express software (PE Applied Biosystems). The primers and probes for 18S rRNA were: forward 5'-CGGCTACCACATCCAAGGAA-3' (SEQ ID NO: 11); reverse 5'-GCTGGAATTACCGCGGCT-3' (SEQ ID NO: 12); and probe 5' -6FAM-TGCTGGCACCAGACTTGCCCTC-TAMRA-3' (SEQ ID NO: 13). The primers and probes for Par-4 were: forward 5'-CCCAGATCCAGGAACCTCCT-3' (SEQ ID NO: 14); reverse 5'-TTTTGTATCTGCCTGGGACTGTT-3' (SEQ ID NO: 15) and probe 5'-6FAM-CCTGCCCCAGGACCCGTCG-TAMRA-3' (SEQ ID NO: 16). For RT-PCR analysis, 1 μl of cDNA was used in a 25 μl reaction mixture in the presence of 200 nM of primers, 100 nM of probe and 0.625 unit of AmpliTaq Gold polymerase. Relative quantitation of Par-4 mRNA and 18S rRNA were calculated using the comparative threshold cycle number for each sample fitted